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**VEGF signaling has distinct spatiotemporal roles during heart valve development.**

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**Public Summary:**

This article describes how a signaling molecule, vascular endothelial growth factor (VEGF), coordinates the interactions between progenitor cells to organize heart valve development.

**Scientific Abstract:**

Heart valve malformations are one of the most common types of birth defects, illustrating the complex nature of valve development. Vascular endothelial growth factor (VEGF) signaling is one pathway implicated in valve formation, however its specific spatial and temporal roles remain poorly defined. To decipher these contributions, we use two inducible dominant negative approaches in mice to disrupt VEGF signaling at different stages of embryogenesis. At an early step in valve development, VEGF signals are required for the full transformation of endocardial cells to mesenchymal cells (EMT) at the outflow tract (OFT) but not atrioventricular canal (AVC) endocardial cushions. This role likely involves signaling mediated by VEGF receptor 1 (VEGFR1), which is highly expressed in early cushion endocardium before becoming downregulated after EMT. In contrast, VEGFR2 does not exhibit robust cushion endocardium expression until after EMT is complete. At this point, VEGF signaling acts through VEGFR2 to direct the morphogenesis of the AVC cushions into mature, elongated valve leaflets. This latter role of VEGF requires the VEGF-modulating microRNA, miR-126. Thus, VEGF roles in the developing valves are dynamic, transitioning from a differentiation role directed by VEGFR1 in the OFT to a morphogenetic role through VEGFR2 primarily in the AVC-derived valves.

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